REMARKS

The May 2, 2003 Official Action and the references cited therein have been carefully reviewed. In view of the amendments submitted herewith and the following remarks, favorable reconsideration and allowance of this application are earnestly solicited.

At page 2 of the Official Action, the Examiner maintains the rejection of claims 1-3 under 35 U.S.C. §112, second paragraph. The Examiner maintains the position that the term "recombinant cell" recited in the claims is indefinite.

At page 2, the Examiner also maintains the rejection of claims 1-3 under 35 U.S.C. §103(a) as allegedly being unpatentable over Lill et al. (June 19, 1997, Nature, Vol. 387, pages 823-27), Gu et al. (June 19, 1997, Nature, Vol. 387, pages 819-823), or Arany et al. (November 1997, Proc. Natl. Acad. Sci. USA, Vol. 93, pages 12969-12973), and further in view of U.S. Patent 5,607,967 and Gurtu et al. (1996, Biochemical and Biophysical Research Communications, Vol. 229, pages 295-298).

The foregoing constitutes the entirety of the rejections raised in the May 2, 2003 Official Action. In light of the present amendments and the following remarks, each of the above-mentioned rejections under 35 U.S.C. §112, second paragraph and 35 U.S.C. §103(a) is respectfully traversed.

No new matter has been introduced into this application by reason of any of the amendments presented herewith.

Please cancel claims 4-8.

CLAIMS 1-3 FULLY COMPLY WITH THE REQUIREMENTS OF 35 U.S.C. §112, SECOND PARAGRAPH

Applicants disagree with the Examiner's assertion that the metes and bounds of the term "recombinant cell" are not clear. However, in order to expedite prosecution, Applicants have amended claims 1 and 3 to further recite that the

recombinant cells are "stably transfected" with the indicated plasmids. Support for these amendments can be found at page 22, line 11 through page 23, line 28. In view of the amendments presented herewith, Applicants have overcome the Examiner's rejection of claims 1-3 under 35 U.S.C. §112, second paragraph and respectfully request its withdrawal.

CLAIMS 1-3 ARE NOT RENDERED OBVIOUS BY THE COMBINATION OF LILL ET AL., GU ET AL., OR ARANY ET AL. AND U.S. PATENT 5,607,967 AND GURTU ET AL.

The Examiner has maintained the rejection of claims 1-3 under 35 U.S.C. §103(a) as allegedly being unpatentable over Lill et al., Gu et al., or Arany et al., and further in view of U.S. Patent No. 5,607,967 (hereinafter, Patent '967) and Gurtu et al. Specifically, the Examiner interprets the term "recombinant cell" as any cell that contains recombinant DNA that is either "transiently expressed or stably expressed" and, therefore, contends that the teaching of only transiently transfected cells by the primary references, i.e., Lill et al., Gu et al., and Arany et al., is irrelevant. The Examiner also maintains that a second reporter gene is taught by the primary references. Additionally, the Examiner claims that Arany et al. show the "involvement of p300/CBP in transactivation of important genes for tumor development," Patent '967 shows the "current state of art using transactivation of [a] reporter gene as a simple way of screening [for] useful compounds," and Gurtu et al. show the "current state of art that making recombinant cell[s] using [a] selective marker is [a] well known technique." The Examiner further asserts that all three primary references suggest that "p300/CBP might be a target for intervention of tumor development." The Examiner concludes that the prior art teaches all the claimed limitations and provides the required motivation for a skilled artisan to arrive at the instant

invention, thereby rendering the instant invention obvious over the cited prior art.

Applicants hereby reiterate that to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claimed limitations (MPEP §2143). Applicants respectfully submit that the Examiner has failed to satisfy the requirements of establishing a *prima facie* case of obviousness.

In the instant case, claims 1 and 3 have been amended to recite recombinant cells that are **stably** transfected with i) a first plasmid expressing a p300/CBP responsive promoter operably linked to a first reporter gene, ii) a second plasmid expressing a non p300/CBP responsive promoter operably linked to a second reporter gene, and iii) a third plasmid expressing a selectable marker gene. They are not obvious over the references cited by the Examiner.

The Examiner asserts that the cited prior art teaches all the claimed limitation and provides motivation for a skilled artisan "to screen useful compounds that **enhance** p300/CBP activity, [to] in turn **enhance** wild type p53 tumor suppressor protein activity to control tumor development or treat cancer."

The present invention, however, is based on Applicants' discovery that p300/CBP is required for the up-regulation of mdm2 by p53 and the inhibition of p53-mediated apoptosis (see page 39, line 21 through page 41, line 22 of the specification). The present claims are, therefore, directed to cell lines and methods for screening compounds that **inhibit**

p300/CBP activity and thereby **induce** apoptosis. Thus, according to the Examiner's own interpretation, the prior art teaches away from the present invention by teaching the exact opposite of the instantly claimed cell lines and methods.

Specifically, Lill et al. teach that E1A, an oncoprotein that binds to p300/CBP, reduces p53-mediated activation of the *p21* and *bax* promoters and suppresses p53-induced cell-cycle arrest and apoptosis. Lill et al. also disclose that wild-type E1A, but not a mutant E1A (Δ2-36 E1A) which can no longer bind p300, "**suppresses** p53-induced apoptosis at early times after transfection" (page 824, right column). Inasmuch as Lill et al. teach that E1A disrupts functions mediated by p53 by binding to p300/CBP (see Abstract) and E1A suppressed p53-induced apoptosis (see page 824, right column), the reference strongly suggests that the inhibition of p300/CBP activity **suppresses** apoptosis. Therefore, Lill et al. teach away from the present invention and can not be properly used to establish a *prima facie* case of obviousness.

Secondly, Gu et al. disclose that p53 interacts with p300/CBP *in vitro* and *in vivo* and that p300/CBP is a p53 coactivator and is "required for optimal p53 mediated transactivation" (Abstract and page 822, left column). Because p53 is known as a tumor suppressor protein whose "ability to inhibit cell growth is dependent upon its transactivation function" (see Abstract), the teachings of Gu et al. suggest inhibition of p300/CBP would inhibit the tumor suppressing activities of p53. The reference in no way teaches or suggests that agents that **inhibit** p300/CBP activity can **induce** apoptosis. In fact, the reference teaches the opposite of Applicants' invention and therefore can not be properly cited employed to establish a *prima facie* case of obviousness.

Thirdly, Applicants disagree with the Examiner's interpretation of Arany et al. The Examiner references the

Abstract of Arany et al. for support for the conclusion that p300/CBP is an "important target for [the] regulation of tumor development." Upon close examination of the Abstract, the only support Applicants can find for the Examiner's conclusion is the statement that "paradoxically, these data ... suggest that p300/CBP are active in both transformation suppression and tumor development." Clearly, this statement falls far short of providing a skilled artisan with the necessary motivation to develop an assay to identify compounds that inhibit p300/CBP activity and induce apoptosis. Indeed, the skilled artisan, based solely on the statement within the Abstract of Arany et al., would conclude any agents found to inhibit the activity of p300/CBP in tumor suppression would contrarily have the undesirable side-effect of inhibiting the p300/CBP activity of transformation suppression. At most, the statement is an invitation for those skilled in the art to further investigate the role of p300/CBP in tumor development. Furthermore, Arany et al. disclose that p300/CBP contributes to vascular endothelial growth factor (VEGF) synthesis which is known to be important for angiogenesis and tumor expansion (see page 12972, right column to page 12973, left column). It is this angiogenesis that Arany et al. asserts is the tumor progression activity of p300/CBP (see page 12973, left column). Thus, Arany et al. simply provide speculation that p300/CBP-HIF complexes might be "a possible target for rational therapy of tumors ... characterized by aberrant hypoxia-induced **neovascularization**" (page 12973, left column). Nowhere in Arany et al. is it taught or speculated that inhibitors of p300/CBP activity can induce **apoptosis**, as opposed to the hypoxia-induced **angiogenesis** discussed throughout Arany et al. A skilled artisan would readily appreciate that the inhibition of **angiogenesis** is not comparable or necessarily related to the induction of **apoptosis**.

Thus, Applicants submit that the three primary references, i.e., Lill et al., Gu et al. and Arany et al., relied on by the Examiner fail to teach or even suggest that p300/CBP inhibitors can induce apoptosis. Furthermore, there is no motivation for those skilled in the art to combine the teachings of any of the primary references with the disclosure of Patent '967 and Gurtu et al. to arrive at the claimed method of screening for agents that inhibit p300/CBP activity and thereby induce apoptosis.

Moreover, Applicants submit that the combined teachings of any one of the primary references and that of Patent '967 and Gurtu et al., do not teach each and every element of the present invention with regard to stably transfected cells containing multiple reporter genes under the control of different promoters. As set forth in the January 27, 2003 response to the September 25, 2002 Official Action, Applicants submit that Patent '967 discloses a method for challenging cells with a panel of compounds and monitoring a reporter gene to assess activation by a chimeric protein. Patent '967, however, clearly fails to describe or suggest transfecting the **same** cells with a second plasmid containing a second reporter gene linked to another promoter element that is not responsive to the chimeric protein. Inasmuch as the Examiner indicates that Patent '967 shows the "current state of art using transactivation of [a] reporter gene ... for screening useful compounds," Applicants conclude the prior art fails to teach or suggest each and every element of the instantly claimed invention.

Additionally, the Examiner has indicated that Gurtu et al. show the "current state of the art that making recombinant cell[s] using [a] selective marker is well known." As noted in the January 27, 2003 response to the September 25, 2002 Official Action, Applicants contend that Gurtu et al. fail to teach the creation of a stable cell line containing **two** or more plasmids containing **two** or more antibiotic resistance

genes for selection. Therefore, Applicants conclude that the prior art fails to teach or suggest each and every element of the instantly claimed invention.

Furthermore, as presented in the January 27, 2003 response, the three primary references the Examiner has relied on fail to teach cells stably transfected with **two** promoter-reporter gene constructs, i.e., a p300/CBP responsive promoter linked to one reporter gene and a non p300/CBP responsive promoter linked to a second reporter gene. The Examiner argues that Lill et al. "teach a control plasmid, which is not activated by p300, i.e. MG_{15}-CAT." Applicants reassert their argument that nowhere in Lill et al. is there a teaching or a suggestion of a **single** recombinant cell comprising the **two** promoter-reporter gene constructs indicated above. The mere suggestion of a non-p300 responsive promoter linked to a reporter gene in no way motivates or suggests to a skilled artisan to transfect into a **single** cell **both** a p300/CBP responsive promoter linked to one reporter gene and a non p300/CBP responsive promoter linked to a second reporter gene, in order to employ the recombinant cell in an assay to identify inhibitory compounds. Additionally, Applicants maintain, as stated in the January 27, 2003 response, that Gu et al. and Arany et al. fail to teach a **single** recombinant cell comprising the **two** promoter-reporter gene constructs indicated above. Applicants also note the Examiner failed to rebut these assertions in the instant Office Action. Therefore, Applicants maintain that the references relied on by the Examiner fail to teach a recombinant cell comprising a p300/CBP responsive promoter linked to one reporter gene and a non p300/CBP responsive promoter linked to a second reporter gene.

Applicants also note that the Examiner has construed a "recombinant cell as any cell containing recombinant DNA no matter whether the recombinant cell is transiently expressed

or stably expressed." As noted hereinabove, Applicants have amended claims 1 and 3 to recite recombinant cells as cells that are **stably** transfected with recombinant DNAs. Since only **transiently** transfected cells are disclosed by the three primary references, the references fail to describe each and every element of the pending claims, as amended.

The Examiner has also asserted that the "primary references teach at least two different reporter genes." However, Applicants submit that although the primary references, such as Lill et al., teach two reporter genes (e.g., CAT and Luc), none of the references teach a **single** recombinant cell line **stably** transfected with **both** a plasmid containing a first reporter gene under the control of a p300/CBP responsive promoter and a plasmid containing the second reporter gene under the control of a non p300/CBP responsive promoter. Specifically, the primary references only teach cells **transiently** transfected with **either** a plasmid containing a p300 responsive promoter linked to a reporter gene (such as PG_{13}-CAT in Lill et al. and Mdm2-Luc in Gu et al.) **or** a plasmid containing a non p300 responsive promoter linked to a reporter gene (such as MG_{15}-CAT in Lill et al.).

In summary, the requirements to establish a *prima facie* case of obviousness have not been met. The references relied upon by the Examiner either do not teach or suggest the present invention or, in fact, teach away from the present invention. Therefore, the references also fail to provide any reasonable expectation of success of the present invention. Inasmuch as the combined disclosure of Lill et al., Gu et al., Arany et al., patent '967, and Gurtu et al. fails to teach each and every element of the claimed invention, Applicants respectfully submit that the rejection of claims 1-3 under 35 U.S.C. §103(a) is untenable and request its withdrawal.

CONCLUSION

It is respectfully requested that the amendments presented herewith be entered in this application, since the amendments are primarily formal, rather than substantive in nature. This amendment is believed to clearly place the pending claims in condition for allowance. In any event, the claims as presently amended are believed to eliminate certain issues and better define other issues which would be raised on appeal, should an appeal be necessary in this case.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number give below.

Respectfully submitted,
DANN, DORFMAN, HERRELL AND SKILLMAN
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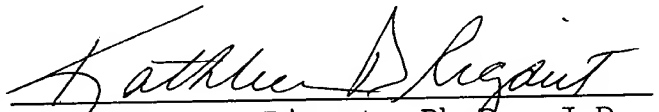
By 
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